REMARKS

Claims 26-32 44, 45, 47, and 48 have been amended and are pending upon entry of this amendment. Claims 33-44 and 46 have been cancelled. Claims 49-56 were added as a result of rewriting multiple dependent claims 28-31 and 44-48 as single-claim dependent claims. Support for claims 26-32, 44, 45, 47, and 48-56 is found throughout the specification as filed including the original claims. Specifically, support for PSGL-1 binding activity and identification of the PSGL-1-binding fragment as the biologically active domain can be found at least at page 9, lines 30-33; page 24, lines 13-26; page 48, lines 8-14; and in Example 4 (pages 73-75). Support for the recitation of "at least 90% identical" can be found at least at page 18, lines 14-20, and page 24, lines 32-38.

Applicants have amended the specification to remove references to a biological deposit and to insert references to the Sequence Listing in compliance with 37 C.F.R. § 1.821(d). Accordingly, Applicants submit a copy of a Sequence Listing which incorporates two additional sequences disclosed in the specification on page 73, at lines 16 and 31. The paper copy of the Sequence Listing is identical to the computer readable form (CFR) also submitted herewith.

Applicants' representative has reviewed the specification for trademarks and has not identified any. If the Examiner is aware of any unidentified trademarks in the specification, Applicants respectfully request that the trademarks be identified so that the specification can be amended accordingly.

In the Drawings, Figure 1 has been relabeled as Figure 1A and 1B to correct informalities noted by the Draftsperson. References to Figure 1 in the specification

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have been amended accordingly. Applicants have filed corrected drawings concurrently with this Amendment.

A marked-up version showing changes made in the replacement paragraphs and the amended claims is attached herewith in compliance with 37 C.F.R. § 1.121. No new matter has been introduced by any of these amendments.

Written Description Rejection under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 26-29, 31-35, and 37-48 as allegedly failing to meet the written description requirement of 35 U.S.C. § 112, first paragraph. Applicants respectfully traverse this rejection.

To establish a *prima facie* case of lack of written description under 35 U.S.C. § 112, first paragraph, the Examiner must show that the specification does not reasonably convey to one skilled in the art that Applicants had possession of the claimed invention. See, e.g., Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991); see also Purdue Pharma L.P. v. Faulding Inc., 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000). The burden is on the Examiner to establish a *prima facie* case of lack of written description. Only if this burden is met, does the burden shift to Applicants to provide rebuttal evidence. In re Wertheim, 541 F.2d 257, 265, 191 USPQ 90, 98 (CCPA 1976); Ex parte Sorenson, 3 USPQ2d 1462, 1463 (Bd. Pat. App. & Inter. 1987). The Examiner has not met this burden here, but rather has done nothing more than to argue lack of literal support. This is not enough to support a written description rejection. In re Wertheim, 541 F.2d 257, 266, 191 USPQ 90, 98 (CCPA 1976).

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According to the Examiner, the specification does not provide adequate written description of "'a SLIC-1 protein,' ... 'at least 90% identical to SEQ ID NO:2,' ... 'comprises' 'a sequence' or 'at least .... contiguous amino acids of ... a sequence or a SEQ ID NO:2.'" Office Action, Nov. 15, 2002, at 2. Applicants respectfully disagree.

The written description consists of the specification and the claims as originally filed. Moreover, the subject matter of a claim need not be described literally (i.e., using the same terms or *in haec verba*) in order to meet the written description requirement. Claim limitations can be supported in the specification through express, implicit, or inherent disclosure. Manual of Patent Examining Procedure (MPEP) § 2163.

Without conceding to the Examiner's position, Applicants have cancelled claims 33-44 and 46, while partially incorporating the subject matter of these claims into pending claims. Applicants reserve the right to pursue the subject matter of the cancelled claims in subsequent applications. Applicants set forth below the basis for written description support of each claim element identified by the Examiner in the Office Action and appearing in the pending claims as amended:

a. "SLIC-1 protein .... comprises at least .... amino acids" and "SLIC-1 protein .... comprises at least .... contiguous amino acids of SEQ ID NO:2"

Written description of SLIC-1 protein that "comprises at least ... contiguous amino acids of SEQ ID NO:2" is found in the specification on page 5, lines13-15, which states:

> [T]he invention features ***fragments*** of the protein having the amino acids sequence SEQ ID NO:2, wherein the fragment ***comprises at least*** 15 ***amino acids*** (e.g., 15 ***contiguous*** amino acids) of the amino acid sequence of SEQ ID NO:2.

(Emphasis added.)

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Applicants note that SEQ ID NO:2 represents a sequence of 316 contiguous amino acids. Therefore, a skilled artisan would recognize that Applicants were in possession of the genus of all contiguous sequences that can be derived from SEQ ID NO:2 because the chemical identity (i.e., exact amino acid sequence) of any species of this genus can be immediately envisaged.

Written description for the specific numbers of contiguous amino acids, recited in claims 28-32, is found in the specification on page 24, lines 22-23, which states that "[a] biologically active portion of a SLIC-1 protein can be a polypeptide which is, for example, 25, 30, 35, 40, 45, 75, 88, 100, 125, 150, 160, 175, 200, 226 or more amino acids in length."

b. "a polypeptide which is at least 90% identical to SEQ ID NO:2"

Written description of "a polypeptide which is at least 90% identical to SEQ ID NO:2" and retains the functional activity of SEQ ID NO:2 is found in the specification on page 24, lines 33-38, which states:

> In other embodiments, the SLIC-1 protein is substantially identical to SEQ ID NO:2, and retains the functional activity of the protein of SEQ ID NO:2, yet differs in amino acid sequence due to natural variation or mutagenesis, as described in detail in subsection I above. Accordingly, in another embodiment, ***the SLIC-1 protein is a protein which comprises an amino acid sequence at least about*** 50%, 55%, 60%, 70%, 75%, 80%, 85%, ***90%,*** 96%, 97%, 98%, 99% ***or more identical to SEQ ID NO:2***.

(Emphasis added.)

The methods for identifying the percent identity are well known in the art and are described on page 25 of the specification. The procedures for making variants of SEQ

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ID NO:2 having at least 90% identity to SEQ ID NO:2 that retain the activity (e.g., binding to PSGL-1 as required by the claims) are conventional in the art. Moreover, the specification discloses actual reduction to practice of (1) the full-length amino acid and nucleotide sequences of SLIC-1, (2) a truncated form of SLIC-1 which retains binding to PSGL-1, and (3) an assay for determining whether a SLIC-1 protein retains the PSGL-1-binding activity. Using the aforementioned assay, Applicants have determined that amino acids 226-316 of SEQ ID NO:2 are not required for binding to PSGL-1, whereas amino acids 1-160 are not sufficient for the binding (page 75, lines 7-12). Given this amount of information about the structure-function relationship, a skilled artisan could readily envisage multiple species within the genus of variants of SEQ ID NO:2 that retain the PSGL-1-binding activity. A skilled artisan would, therefore, conclude that Applicants were in possession of the genus of polypeptides that are at least 90% identical to SEQ ID NO:2 and are capable of binding to PSGL-1.

As a case in point, Example 14 of the Revised Interim Written Description Guidelines Training Materials illustrates the application of the written description requirement to the following generic claim: "A protein having SEQ ID NO: 3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A–>B." Revised Interim Written Description Guidelines Training Materials, at 53. According to the Training Materials, a generic claim similar to Example 14 would be adequately described under 35 U.S.C. § 112, first paragraph, because: "[t]he single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound, and because of the limitation requiring the stated compounds to catalyze the reaction of A–>B" (emphasis added). Id.

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If the claim in the Training Material satisfy the written description requirement, claims 26-32 and 44-48 should also satisfy this requirement in light of the greater structural details provided by Applicants' disclosure.

The Examiner further alleges that there does not appear sufficient written description of the additional sequences associated with the claimed SLIC-1 proteins or polypeptides that do not contain the entire protein. Office Action, at 3. Applicants note that the specification does describe, *inter alia*, T7, GST, maltose E-binding protein, and protein A as examples of entities that may be fused to SLIC-1, all of which are conventional in the art. Claims 47 and 48 recite GST and T7, accordingly. The specification discloses actual reduction to practice of several T7-fused forms of SLIC-1 in Example 4. Written description of GST and T7 can further be found in the specification, for example, on page 26, lines 25-29, which states:

> For example, in one embodiment, the fusion protein is a GST-SLIC-1 fusion protein in which the SLIC-1 sequences are fused to the C-terminus of the GST sequences. In another embodiment, the fusion protein is a T7-SLIC-1 fusion protein in which the SLIC-1 sequences are fused to T7 sequences, e.g., a T7 protein tag (see Example 4).

Thus, the specification provides sufficient support for sequences associated with SLIC-1.

c. "SLIC-1 protein ... comprises a PSGL-1-binding fragment"

Written description of "SLIC-1 protein [which] comprises a PSGL-1-binding fragment" can be found in Example 4, which discloses actual reduction to practice of a truncated form of SLIC-1 comprising of a PSGL-1-binding fragment of SEQ ID NO:2. Additional support can be found in other parts of the specification as follows:

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> As used herein, the term, [sic] "selectin ligand interactor cytoplasmic-1" or "***SLIC-1" molecule includes a protein or polypeptide which binds to or interacts with the cytoplasmic domain of a selectin glycoprotein ligand (e.g., PSGL-1)***... (Page 8, lines 19-23, emphasis added.)
>
> As used herein, a "selectin ligand interactor cytoplasmic-1 molecule activity" or a "***SLIC-1 activity*** ***includes an activity which involves binding or interacting with the cytoplasmic domain of a selectin glycoprotein ligand (e.g., PSGL-1)*** or a selectin protein and transducing a signal, e.g., via an effector molecule. In addition, a SLIC-1 activity includes an activity which involves mediating the interaction of a protein (e.g., PSGL-1) with the cytoskeleton. (Page 9, lines 30-35, emphasis added.)
>
> As used herein, a "biologically active portion" of a SLIC-1 protein includes ***a fragment of a SLIC-1 protein which participates in an interaction between a SLIC-1 molecule and a non-SLIC-1 molecule***. Biologically active portions of a SLIC-1 protein include peptides ***comprising amino acid sequences sufficiently identical to or derived from the amino acid sequence of the SLIC-1 protein***, e.g., the amino acid sequence shown in SEQ ID NO:2, which ***include less amino acids than the full length SLIC-1 proteins, and exhibit at least one activity of a SLIC-1 protein***. (Page 24, lines 13-19, emphasis added.)

As mentioned above, the specification discloses that amino acids 226-316 of SEQ ID NO:2 are not required for binding to PSGL-1, whereas amino acids 1-160 are not sufficient for the binding (page 75, lines 7-12). Given this amount of information about the structure-function relationship and the disclosed actual reduction to practice, a skilled artisan could immediately envisage various length fragments of SEQ ID NO:2 and variants thereof that are expected to retain PSGL-1-binding. A skilled artisan would be easily able to determine whether a fragment binds to PSGL-1 using, for example, procedures illustrated in Example 4. A skilled artisan would, therefore, conclude that Applicants were in possession of the genus of all PSGL-1-binding fragments derived from SLIC-1.

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Applicants note that in order to comply with the written description requirement, a specification need not describe the claimed invention in *ipsis verbis*. In re Edwards, 568 F.2d 1349, 1351-52, 196 USPQ 465, 467 (CCPA 1978). The present specification, therefore, reasonably conveys to a skilled artisan that Applicants were in possession of the invention as claimed. The Examiner has not met the burden of establishing a *prima facie* case of lack of written description. Therefore, Applicants request the Examiner to withdraw the written description rejection.

Enablement Rejection under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 26-29, 31-35, and 37-48, alleging that the specification does not reasonably provide enablement for any "'a SLIC-1 protein or polypeptide' including 'at least 90% identical to SEQ ID NO:2' ... 'comprises' 'a sequence' or 'at least .... contiguous amino acids of ... a sequence or a SEQ ID NO'." Office Action, at 5. The Examiner further rejected claims 26-46, alleging that the specification does not reasonably provide enablement for "any 'activity of said SLIC-1 protein'." Id. The enablement rejection is improper and should be withdrawn.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosure coupled with information known in the art without undue experimentation. United Stated v. Telectronics, Inc., 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988); In re Stephens, 188 USPQ 659 (CCPA 1976). The test for enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. In re Angstadt, 190 USPQ 214 (CCPA 1976), emphasis added. Non-critical features of the invention may be supported by a more

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general disclosure than those at the heart of the invention. In re Stephens, 180 USPQ 659 (CCPA 1976).

The Examiner has the initial burden of giving reasons, supported by the record as a whole, why the specification is not enabling. In re Angstadt, supra. In the present case, the Examiner has not met this burden. Although the Examiner may have demonstrated that some experimentation is necessary, doing so is not enough to shift the burden to applicants to prove that such experimentation is not undue. Id.

In support of the enablement rejection, the Examiner cited three references (Kuntz, Skolnick, and Ngo), which supposedly show that the art is unpredictable. Applicants respectfully submit that the cited references are not pertinent to the claims for the reasons set forth below.

The first reference, Kunz, discusses an iterative approach in drug design which is based on computerized modeling of drug-substrate complexes. Kunz is not relevant because the claims of the present application do not require that the compound which is tested be a drug or otherwise *a priori* possess any specific properties. The claims are directed to methods of identifying a compound which inhibits/increases binding of a SLIC-1 protein to PSGL-1. Antibodies to PSGL-1 and SLIC-1 are nonlimiting examples of compounds that may be tested and these are available commercially or can be produced without undue experimentation. See, e.g., In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The second reference cited by the Examiner, Skolnick, is concerned with predicting a function of a newly discovered gene for which no function is known. The

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article describes a methodology for ascribing a function to a putative protein by comparing the protein's predicted three-dimensional structure with known structures of other proteins for which function has already been established. Skolnick suggests that such a methodology may yield inaccurate results because a tertiary structure of a protein is not necessarily indicative of its function. The problem discussed in Skolnick is not applicable to the present disclosure. To practice the claimed invention, one does not need to rely on theoretical models for structure prediction. As disclosed in the specification, SLIC-1 was actually isolated, cloned and experimentally determined to bind PSGL-1 – no theoretical modeling was involved. Hence, there is no need for theoretical function prediction; here, the function has been established empirically and is a given.

Ngo, the third reference cited by the Examiner, is concerned with the problem of finding an algorithm for predicting the structure of a given protein based on the amino acid sequence alone. *See* page 492, *Future Work*. Although the general problem of predicting a secondary/tertiary protein structure may be of a great scientific import, Applicants submit that one does not need to know what that structure is in order to make and use their invention. Therefore, similarly to Skolnick, Ngo is not applicable here.

Therefore, Kuntz, Skolnick, and Ngo do not provide support for the unpredictability of the pertinent art. To the contrary, Skolnick, for example, suggests that homologous proteins should have similar structures by stating that:

> ***[F]or proteins whose sequence identity is above ~30%, one can use homology modeling*** to build the structure[44]. However, structure prediction is far more difficult for proteins

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> that are not homologous to protein with known structures. Page 36, The State of The Art in Structure-Prediction Methods.

(Emphasis added.)

Applicants respectfully submit an excerpt from Fersht (Structure and Mechanism in Protein Science, W. H. Freeman and Company, N.Y, 1998, page 33-34) which states:

> An important question is: What is the relationship between percent identity and similarity of tertiary structure? This depends on the length of the protein: ***the longer the protein, the lower the percent identity that implies identical structure***. ***For a protein of 85 residues, a 25 to 30% sequence identity implies an three-dimensional identical structure***. Page 34.

Therefore, given that (1) the three-dimensional structure of the genus of 90% identical proteins is expected to be also identical, (2) the function associated with that structure has been experimentally established, and (3) the percent identity is well within the ranges recited in Fersht, a skilled artisan would reasonably believe that a considerable number of species in the claimed genus would retain the function.

It is well known that, in some cases, even a single point mutation may result in a loss of function. It is, however, far more likely, statistically, and is commonly observed that a function is retained even when a significant number of amino acids has been deleted or otherwise mutated. The present specification illustrates this point perfectly. In Example 4 of the specification, even though about one third of all amino acids (90 out of 316) were deleted, the truncated SLIC-1 protein retained the ability to bind PSGL-1. Mutated SLIC-1 proteins can reasonably be expected to retain the PSGL-1-binding activity and can be made using techniques conventional in the art. For example, Fersht states that "[t]here are simple rules, however, to produce mutants that have a chance of

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being analyzed simply" (page 425, enclosed). If a nonfunctional variant exists, it does not render a claim nonenabled. Atlas Powder Co. v. E.I. duPont de Nemous & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984). The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. The procedure that can be used to determine whether a fragment binds to PSGL-1 is described in Example 4. Considering this Example and the level of skill and knowledge in the art, one skilled in the art would be able to make SLIC-1 proteins required to practice the claims methods within their full scope. Thus, the primary structure disclosed in the specification fully satisfies the enablement requirement. Moreover, screening methods are routine in art. See, e.g., Ligand-Binder Assays: Labels and Analytical Strategies, Kricka, L., Macel Dekker, Inc., N.Y., 1985, pages 1-3, enclosed. Considering the state of the art in the screening procedures and the disclosure of the screening assays in the specification on pages 47-52, a skilled artisan would be able to practice the two steps of claims 26 and 27 ((i) contacting said SLIC-1 protein with a test compound and (ii) determining the effect of the test compound on the binding of said SLIC-1 protein to PSGL-1) without undue experimentation.

In conclusion, one skilled in the art could make and use the claimed invention from the disclosure coupled with information known in the art without undue experimentation. The Examiner has not met the burden of establishing that undue experimentation is required. Therefore, Applicants request the Examiner to withdraw the enablement rejection.

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Rejection under 35 U.S.C. § 112, Second Paragraph

The Examiner rejected claims 26-48 under 35 U.S.C. § 112, second paragraph, as indefinite because of the term "activity," which is allegedly ambiguous and ill-defined.

Without conceding to the Examiner's position, Applicants have amended claims 26-48. Claims as amended recite "binding of a SLIC-1 protein to PSGL-1." Accordingly, Applicants request the Examiner to withdraw the indefiniteness rejection.

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to deposit account 06-0916.

Respectfully submitted,
FINNEGAN, HENDERSON,
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Dated: April 8, 2003

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VERSION WITH MARKINGS SHOWING CHANGES MADE

IN THE SPECIFICATION:

Replace the five paragraphs beginning on page 3, at line 19, and ending on page 4, at line 23, with the following five paragraphs:

-- In one embodiment, a SLIC-1 nucleic acid molecule of the invention is at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more identical to the nucleotide sequence (e.g., to the entire length of the nucleotide sequence) shown in SEQ ID NO:1 ~~or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~, or a complement thereof. In a preferred embodiment, the isolated nucleic acid molecule includes the nucleotide sequence shown in SEQ ID NO:1, or a complement thereof. In another preferred embodiment, the nucleic acid molecule consists of the nucleotide sequence shown in SEQ ID NO:1. In another preferred embodiment, the nucleic acid molecule includes a fragment of at least 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, or 900 nucleotides (e.g., contiguous nucleotides) of the nucleotide sequence of SEQ ID NO: 1, or a complement thereof.

In another embodiment, a SLIC-1 nucleic acid molecule includes a nucleotide sequence encoding a protein having an amino acid sequence sufficiently identical to the amino acid sequence of SEQ ID NO:2 ~~or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~. In a preferred embodiment, a SLIC-1 nucleic acid molecule includes a nucleotide sequence encoding a protein having an amino acid sequence at least 50%, 55%, 60%, 65%, 70%,

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75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more identical to the entire length of the amino acid sequence of SEQ ID NO:2 or the amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number _____.

In another preferred embodiment, an isolated nucleic acid molecule encodes the amino acid sequence of human SLIC-1. In yet another preferred embodiment, the nucleic acid molecule includes a nucleotide sequence encoding a protein having the amino acid sequence of SEQ ID NO:2, or the amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number _____. In yet another preferred embodiment, the nucleic acid molecule is at least 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, or 900 nucleotides in length. In a further preferred embodiment, the nucleic acid molecule is at least 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, or 900 nucleotides in length and encodes a protein having a SLIC-1 activity (as described herein).

Another embodiment of the invention features nucleic acid molecules, preferably SLIC-1 nucleic acid molecules, which specifically detect SLIC-1 nucleic acid molecules relative to nucleic acid molecules encoding non-SLIC-1 proteins. For example, in one embodiment, such a nucleic acid molecule is at least 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900 or more nucleotides in length and hybridizes under stringent conditions to a nucleic acid molecule comprising the nucleotide sequence shown in SEQ ID NO:1, the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____, or a complement thereof.

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In other preferred embodiments, the nucleic acid molecule encodes a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:2 ~~or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~, wherein the nucleic acid molecule hybridizes to a nucleic acid molecule comprising SEQ ID NO:1 under stringent conditions --.

Replace the paragraph beginning on page 5, at line 1, with the following paragraph:

-- In a preferred embodiment, a SLIC-1 protein includes at least one immunoreceptor tyrosine-based activation motif and has an amino acid sequence at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence of SEQ ID NO:2~~, or the amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~ --.

Replace the paragraph beginning on page 5, at line 13, with the following paragraph:

-- In another embodiment, the invention features fragments of the protein having the amino acid sequence of SEQ ID NO:2, wherein the fragment comprises at least 15 amino acids (e.g., 15 contiguous amino acids) of the amino acid sequence of SEQ ID NO:2~~, or an amino acid sequence encoded by the DNA insert of the plasmid deposited with the ATCC as Accession Number _____~~. In one embodiment, a SLIC-1 protein has amino acid residues 1-88 of SEQ ID NO:2. In another embodiment, a SLIC-1 protein has amino acid residues 1-60 of SEQ ID NO:2. In a further embodiment, a SLIC-

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1 protein has amino acid residues 1-226 of SEQ ID NO:2. In another embodiment, a SLIC-1 protein has the amino acid sequence of SEQ ID NO:2 --.

Replace the paragraph beginning on page 7, at line 9, with the following paragraph:

-- *Figures 1A and 1B* depicts the cDNA sequence and predicted amino acid sequence of human SLIC-1. The nucleotide sequence corresponds to nucleic acids 1 to 951 of SEQ ID NO:1. The amino acid sequence corresponds to amino acids 1 to 316 of SEQ ID NO: 2 --.

On pages 11 and 12, replace the bridging paragraph beginning on page 11 at line 33 with the following paragraph:

-- The nucleotide sequence of the isolated human SLIC-1 cDNA and the predicted amino acid sequence of the human SLIC-1 polypeptide are shown in Figures 1A and 1B and in SEQ ID NOs:1 and 2, respectively. ~~A plasmid containing the nucleotide sequence encoding human SLIC-1 was deposited with the American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, Va. 20110-2209, on _____ and assigned Accession Number _____. This deposit will be maintained under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure. This deposit was made merely as a convenience for those of skill in the art and is not an admission that a deposit is required under 35 U.S.C. § 112.~~ --.

Replace the two paragraphs beginning on page 12, at line 35, and ending on page 13, at line 13, with the following two paragraphs:

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-- A nucleic acid molecule of the present invention, e.g., a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:1, ~~or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~, or a portion thereof, can be isolated using standard molecular biology techniques and the sequence information provided herein. Using all or portion of the nucleic acid sequence of SEQ ID NO:1, ~~or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~, as a hybridization probe, SLIC-1 nucleic acid molecules can be isolated using standard hybridization and cloning techniques (e.g., as described in Sambrook, J., Fritsh, E. F., and Maniatis, T. Molecular Cloning: A Laboratory Manual. 2nd, ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989) .

Moreover, a nucleic acid molecule encompassing all or a portion of SEQ ID NO:1, ~~or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~ can be isolated by the polymerase chain reaction (PCR) using synthetic oligonucleotide primers designed based upon the sequence of SEQ ID NO:1, ~~or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~ --.

Replace the three paragraphs beginning on page 13, at line 24, and ending on page 14, at line 26, with the following three paragraphs:

-- In another preferred embodiment, an isolated nucleic acid molecule of the invention comprises a nucleic acid molecule which is a complement of the nucleotide sequence shown in SEQ ID NO:1, ~~or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~, or a portion of any of

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these nucleotide sequences. A nucleic acid molecule which is complementary to the nucleotide sequence shown in SEQ ID NO:1, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____, is one which is sufficiently complementary to the nucleotide sequence shown in SEQ ID NO:1, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____, such that it can hybridize to the nucleotide sequence shown in SEQ ID NO:1, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____, thereby forming a stable duplex.

In still another preferred embodiment, an isolated nucleic acid molecule of the present invention comprises a nucleotide sequence which is at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more identical to the entire length of the nucleotide sequence shown in SEQ ID NO:1, or the entire length of the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____, or a portion of any of these nucleotide sequences.

Moreover, the nucleic acid molecule of the invention can comprise only a portion of the nucleic acid sequence of SEQ ID NO:1, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____, for example, a fragment which can be used as a probe or primer or a fragment encoding a portion of a SLIC-1 protein, e.g., a biologically active portion of a SLIC-1 protein. The nucleotide sequence determined from the cloning of the SLIC-1 gene allows for the generation of probes and primers designed for use in identifying and/or cloning other SLIC-1 family members, as well as SLIC-1 homologues from other species. The probe/primer typically comprises substantially purified oligonucleotide. The oligonucleotide typically

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comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 12 or 15, preferably about 20 or 25, more preferably about 30, 35, 40, 45, 50, 55, 60, 65, 75, 80, 85, 90, 95, 100, 150, or 200 or more consecutive nucleotides of a sense sequence of SEQ ID NO: 1, ~~or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~, of an anti-sense sequence of SEQ ID NO:1, ~~or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~, or of a naturally occurring allelic variant or mutant of SEQ ID NO: 1, ~~or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number~~. In one embodiment, a nucleic acid molecule of the present invention comprises a nucleotide sequence which is greater than 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900 or more nucleotides in length and hybridizes under stringent hybridization conditions to a nucleic acid molecule of SEQ ID NO:1, ~~or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~ --.

Replace the three paragraphs beginning on page 14, at line 35, and ending on page 15, at line 21, with the following three paragraphs:

-- A nucleic acid fragment encoding a "biologically active portion of a SLIC-1 protein" can be prepared by isolating a portion of the nucleotide sequence of SEQ ID NO:1, ~~or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~, which encodes a polypeptide having a SLIC-1 biological activity (the biological activities of the SLIC-1 proteins are described herein), expressing the encoded portion of the SLIC-1 protein (e.g., by recombinant expression in vitro) and assessing the activity of the encoded portion of the SLIC-1 protein.

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The invention further encompasses nucleic acid molecules that differ from the nucleotide sequence shown in SEQ ID NO:1~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~, due to degeneracy of the genetic code and thus encode the same SLIC-1 proteins as those encoded by the nucleotide sequence shown in SEQ ID NO:1~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~. In another embodiment, an isolated nucleic acid molecule of the invention has a nucleotide sequence encoding a protein having an amino acid sequence shown in SEQ ID NO:2.

In addition to the SLIC-1 nucleotide sequences shown in SEQ ID NO:1~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~, it will be appreciated by those skilled in the art that DNA sequence polymorphisms that lead to changes in the amino acid sequences of the SLIC-1 proteins may exist within a population (e.g., the human population). Such genetic polymorphism in the SLIC-1 genes may exist among individuals within a population due to natural allelic variation. As used herein, the terms "gene" and "recombinant gene" refer to nucleic acid molecules which include an open reading frame encoding a SLIC-1 protein, preferably a mammalian SLIC-1 protein, and can further include non-coding regulatory sequences, and introns --.

Replace the paragraph beginning on page 16, at line 3, with the following paragraph:

-- Moreover, nucleic acid molecules encoding other SLIC-1 family members and, thus, which have a nucleotide sequence which differs from the SLIC-1 sequences of

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SEQ ID NO: 1, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____ are intended to be within the scope of the invention. For example, another SLIC-1 cDNA can be identified based on the nucleotide sequence of human SLIC-1. Moreover, nucleic acid molecules encoding SLIC-1 proteins from different species, and which, thus, have a nucleotide sequence which differs from the SLIC-1 sequences of SEQ ID NO: 1, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____ are intended to be within the scope of the invention. For example, a mouse SLIC-1 cDNA can be identified based on the nucleotide sequence of a human SLIC-1 --.

Replace the paragraph beginning on page 16, at line 21, with the following paragraph:

-- Accordingly, in another embodiment, an isolated nucleic acid molecule of the invention is at least 15, 20, 25, 30 or more nucleotides in length and hybridizes under stringent conditions to the nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____. In other embodiment, the nucleic acid is at least 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900 or more nucleotides in length --.

Replace the bridging paragraph beginning on page 17, at line 35, with the following paragraph:

-- In addition to naturally-occurring allelic variants of the SLIC-1 sequences that may exist in the population, the skilled artisan will further appreciate that changes can be introduced by mutation into the nucleotide sequences of SEQ ID NO:1, or the

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nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____, thereby leading to changes in the amino acid sequence of the encoded SLIC-1 proteins, without altering the functional ability of the SLIC-1 proteins. For example, nucleotide substitutions leading to amino acid substitutions at "non-essential" amino acid residues can be made in the sequence of SEQ ID NO:1, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____. A "non-essential" amino acid residue is a residue that can be altered from the wild-type sequence of SLIC-1 (e.g., the sequence of SEQ ID NO:2) without altering the biological activity, whereas an "essential" amino acid residue is required for biological activity. For example, amino acid residues that are conserved among the SLIC-1 proteins of the present invention, e.g., those present in a immunoreceptor tyrosine-based activation motif, are predicted to be particularly unamenable to alteration. Furthermore, additional amino acid residues that are conserved between the SLIC-1 proteins of the present invention and other members of the SLIC family are not likely to be amenable to alteration --.

Replace the bridging paragraph beginning on page 18, at line 21, with the following paragraph:

-- An isolated nucleic acid molecule encoding a SLIC-1 protein identical to the protein of SEQ ID NO:2, can be created by introducing one or more nucleotide substitutions, additions or deletions into the nucleotide sequence of SEQ ID NO:1, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____, such that one or more amino acid substitutions, additions or deletions are introduced into the encoded protein. Mutations can be introduced into

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SEQ ID NO:1, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____ by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. Preferably, conservative amino acid substitutions are made at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Thus, a predicted nonessential amino acid residue in a SLIC-1 protein is preferably replaced with another amino acid residue from the same side chain family. Alternatively, in another embodiment, mutations can be introduced randomly along all or part of a SLIC-1 coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for SLIC-1 biological activity to identify mutants that retain activity. Following mutagenesis of SEQ ID NO:1, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____, the encoded protein can be expressed recombinantly and the activity of the protein can be determined --.

Replace the paragraph beginning on page 21, at line 8, with the following paragraph:

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-- In still another embodiment, an antisense nucleic acid of the invention is a ribozyme. Ribozymes are catalytic RNA molecules with ribonuclease activity which are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. Thus, ribozymes (e.g., hammerhead ribozymes (described in Haselhoff and Gerlach (1988) Nature 334:585-591)) can be used to catalytically cleave SLIC-1 mRNA transcripts to thereby inhibit translation of SLIC-1 mRNA. A ribozyme having specificity for a SLIC-1-encoding nucleic acid can be designed based upon the nucleotide sequence of a SLIC-1 cDNA disclosed herein (i.e., SEQ ID NO:1~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~). For example, a derivative of a Tetrahymena L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved in a SLIC-1-encoding mRNA. See, e.g., Cech et al. U.S. Pat. No. 4,987,071; and Cech et al. U.S. Pat. No. 5,116,742. Alternatively, SLIC-1 mRNA can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules. See, e.g., Bartel, D. and Szostak, J. W. (1993) Science 261:1411-1418 --.

Replace the bridging paragraph beginning on page 37, at line 36, with the following paragraph:

-- A transgenic animal of the invention can be created by introducing a SLIC-1-encoding nucleic acid into the male pronuclei of a fertilized oocyte, e.g., by microinjection, retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal. The SLIC-1 cDNA sequence of SEQ ID NO:1 can be introduced as a transgene into the genome of a non-human animal.

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Alternatively, a nonhuman homologue of a human SLIC-1 gene, such as a mouse or rat SLIC-1 gene, can be used as a transgene. Alternatively, a SLIC-1 gene homologue, such as another SLIC-1 family member, can be isolated based on hybridization to the SLIC-1 cDNA sequences of SEQ ID NO:1, ~~or the DNA insert of the plasmid deposited with ATCC as Accession Number _____ (described further in subsection I above)~~ and used as a transgene. Intronic sequences and polyadenylation signals can also be included in the transgene to increase the efficiency of expression of the transgene. A tissue-specific regulatory sequence(s) can be operably linked to a SLIC-1 transgene to direct expression of a SLIC-1 protein to particular cells. Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Pat. Nos. 4,736,866 and 4,870,009, both by Leder et al., U.S. Pat. No. 4,873,191 by Wagner et al. and in Hogan, B., Manipulating the Mouse Embryo, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986). Similar methods are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence of a SLIC-1 transgene in its genome and/or expression of SLIC-1 mRNA in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying a transgene encoding a SLIC-1 protein can further be bred to other transgenic animals carrying other transgenes --.

Replace the paragraph beginning on page 57, at line 14, with the following paragraph:

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-- An exemplary method for detecting the presence or absence of SLIC-1 protein or nucleic acid in a biological sample involves obtaining a biological sample from a test subject and contacting the biological sample with a compound or an agent capable of detecting SLIC-1 protein or nucleic acid (e.g., mRNA, or genomic DNA) that encodes SLIC-1 protein such that the presence of SLIC-1 protein or nucleic acid is detected in the biological sample. A preferred agent for detecting SLIC-1 mRNA or genomic DNA is a labeled nucleic acid probe capable of hybridizing to SLIC-1 mRNA or genomic DNA. The nucleic acid probe can be, for example, the SLIC-1 nucleic acid set forth in SEQ ID NO:1, ~~or the DNA insert of the plasmid deposited with ATCC as Accession Number~~ _____, or a portion thereof, such as an oligonucleotide of at least 15, 30, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to SLIC-1 mRNA or genomic DNA. Other suitable probes for use in the diagnostic assays of the invention are described herein --.

Replace the paragraph beginning on page 72, at line 15, with the following paragraph:

-- Accordingly, the invention is based, at least in part, on the discovery of a human gene encoding a novel protein, referred to herein as SLIC-1. The nucleotide sequence encoding the human SLIC-1 protein is shown in Figures 1A and 1B and is set forth as SEQ ID NO:1. The protein encoded by this nucleic acid comprises about 316 amino acids and has the amino acid sequence shown in Figures 1A and 1B and set forth as SEQ ID NO:2. ~~Clone Uran-5, comprising the coding region of human SLIC-1 was deposited with the American Type Culture Collection (ATCC.RTM.), 10801 University~~

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Boulevard, Manassas, Va. 20110-2209. on _____, and assigned Accession No. _____. --.

Replace the paragraph beginning on page 73, at line 11, with the following paragraph:

-- The nitrocellulose membranes were blocked at 4°C overnight in 3% BSA (SIGMA) in Tris Buffered Saline (TBS) with 0.1% Tween-20. The membranes were washed for 7 minutes in TBS-0.1% Tween, and then incubated for 1 hour in a 1:2500 dilution of affinity-purified rabbit anti-SLIC-1 polyclonal antibodies (Research Genetics, Inc.). These antibodies were generated by immunizing rabbits with a polypeptide antigen having the amino acid sequence QERLEESQLRRPTPR (SEQ ID NO:5) conjugated to KLH. The membranes were washed three times in TBS-0.1% Tween, incubated for 1 hour with a secondary antibody to detect rabbit immunoglobulin, and developed using the ECL Western Blotting Detection System (Amersham). Mock transfections and Western blot analysis using unrelated purified polyclonal rabbit IgG (Serotec) were performed in parallel as controls. The results of this analysis are shown in Figure 2. The SLIC-1 protein exhibits an apparent molecular weight of approximately 45 kD by SDS-PAGE analysis --.

Replace the bridging paragraph beginning on page 73, at line 27, with the following paragraph:

-- A DNA construct that allows the expression of full length SLIC-1 as a fusion protein with a T7 protein tag was generated as follows. A mutated primer for the 5' sequence of SLIC-1 was designed to introduce a T7 tag directly upstream of the initiation codon of SLIC-1 in vector pED.Uran-5 by PCR. The T7 tag encodes the amino

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acid sequence MASMTGGQQMG (SEQ ID NO:6). The PCR reaction generated a product of approximately 380 bp, spanning the N-terminal end of SLIC-1 beyond an AscI restriction site. A 5' SalI site and this AscI site were used to replace the original N-terminal end of SLIC-1 in pED.Uran-5 with the PCR product containing the T7 tag. The resulting vector was designated pED.T7Uran-5 and encodes all 316 amino acids of SLIC-1. The pED.T7Uran-5 vector was further used to create three truncated forms of SLIC-1 as follows. The vector pED.T7U5AA226 encodes for the first 226 amino acids of SLIC-1, and was generated by restriction digestion of pED.T7Uran-5 with NotI and AscI and ligation of the plasmid with a NotI/XbaI linker that also comprises a Stop codon to terminate transcription. A similar approach was used to create pED.T7U5AA160, a 160 amino acid short form of SLIC-1 that was generated by restriction digestion of pED.T7Uran-5 with AscI and XbaI and ligation with an appropriate linker. The vector PED.T7U5AA88 was generated by PCR using the original 5' primer for pED.T7Uran-5 and a newly designed 3' primer which introduced a Stop codon and an additional XbaI site after amino acid residue 88 in SLIC-1. The XbaI and SalI sites in pED.T7Uran-5 were then used to replace the sequence for full length SLIC-1 with this truncated form--.

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IN THE CLAIMS:

26. (Twice Amended) A method for identifying a compound which inhibits the binding ~~activity~~ of a SLIC-1 protein to PSGL-1, comprising:

i) contacting said SLIC-1 protein with a test compound; and

ii) determining the effect of the test compound on the binding ~~activity~~ of said SLIC-1 protein to PSGL-1;

wherein said SLIC-1 protein comprises a PSGL-1-binding fragment of a polypeptide which is at least 90% identical to SEQ ID NO:2.

27. (Amended) A method for identifying a compound which increases the binding ~~activity~~ of a SLIC-1 protein to PSGL-1, comprising:

i) contacting said SLIC-1 protein with a test compound; and

ii) determining the effect of the test compound on binding ~~activity~~ of said SLIC-1 protein to PSGL-1;

wherein said SLIC-1 protein comprises a PSGL-1-binding fragment of a polypeptide which is at least 90% identical to SEQ ID NO:2.

28. (Amended) The method of claim 26 , wherein said SLIC-1 protein comprises at least 150 contiguous amino acids of SEQ ID NO:21.

29. (Amended) The method of claim 28, wherein said SLIC-1 protein comprises at least 200 contiguous amino acids of SEQ ID NO:21.

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30. (Amended) The method of claim 29, wherein said SLIC-1 protein comprises the amino acid sequence of SEQ ID NO:21.

31. (Amended) The method as in claim 26, wherein said SLIC-1 protein comprises at least 150 ~~contiguous~~ amino acids of the polypeptide ~~a sequence~~ which is at least 90% identical to SEQ ID NO:2.

32. (Amended) The method of claim 31, wherein said SLIC-1 protein comprises at least 200 ~~contiguous~~ amino acids of the polypeptide ~~a sequence~~ which is at least 90% identical to SEQ ID NO:2.

44. (Amended) The method as in claim 26, wherein said ~~polypeptide~~ SLIC-1 protein comprises residues 160 to 226 of SEQ ID NO:2.

45. (Amended) The method as in claim 26, wherein said ~~polypeptide~~SLIC-1 protein ~~comprises~~ residues 1 to 226 of SEQ ID NO:2.

47. (Amended) The method as in claim 26, wherein said SLIC-1 protein ~~polypeptide~~ is fused to GST.

48. (Amended) The method as in claim 26, wherein said SLIC-1 protein ~~polypeptide~~ is fused to a T7 protein tag.

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49. (New) The method as in claim 27, wherein said SLIC-1 protein comprises residues 160 to 226 of SEQ ID NO:2.

50. (New) The method as in claim 27, wherein said SLIC-1 protein comprises residues 1 to 226 of SEQ ID NO:2.

51. (New) The method as in claim 27, wherein said SLIC-1 protein is fused to GST.

52. (New) The method as in claim 27, wherein said SLIC-1 protein is fused to a T7 protein tag.

53. (New) The method as in claim 27, wherein said SLIC-1 protein comprises at least 150 contiguous amino acids of SEQ ID NO:2.

54. (New) The method as in claim 53, wherein said SLIC-1 protein comprises at least 200 contiguous amino acids of SEQ ID NO:2.

55. (New) The method as in claim 54, wherein said SLIC-1 protein comprises the amino acid sequence of SEQ ID NO:2.

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56. (New) The method as in claim 27, wherein said SLIC-1 protein comprises at least 150 amino acids of the polypeptide which is at least 90% identical to SEQ ID NO:2.

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